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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,385	07/06/2001	Joyce A. Deleo	DC-0156	4729

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EXAMINER	
JAGOE, DONNA A	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/857,385	DELEO ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 24, 2007 has been entered.

Applicants' arguments filed January 24, 2007 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim 1 is pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In particular, "not to exceed a total dose of 2 mg/kg each day" (present claim 1) is a concept that was not present in the specification as originally filed. The Examiner contends that such dosage limitation was not present in the specification as originally filed.

The specification as originally filed contains the following disclosures concerning methotrexate dosages:

(i) "methotrexate shown to be effective in these studies was low, 1 mg/kg. Clinical experience with methotrexate is widespread, with doses used dependent on the desired clinical effect, and doses ranging as high as 250 mg/kg when used as a chemotherapeutic agent and as low as 0.I mg/kg when used to treat rheumatoid arthritis." (page 8, lines 14-19);

(ii) "...The methotrexate dose administered to rats in the present invention, 1 mg/kg, was one quarter of the maximally tolerated dose for rats." (page 8, lines 22-23);

(iii) "...Group A rats received 1 mg/kg of methotrexate (volume 100 ul/kg) by injecting through a PE-10 catheter through an incision in the exposed dura mater to a position 3 cm central to the incision. The PE-10 catheter was pulled out and the same dose and volume of methotrexate (1 mg/kg) was administered around the injured nerve roots (total dose 2 mg/kg)." (page 9, lines 22-28);

The above disclosures, however, do not provide adequate support for a methotrexate dosage "not to exceed a total dose of 2mg/kg each day". The example above in (iii) does not state to give the methotrexate in a "dose not to exceed 2 mg/kg". It states that the total dose given was 2 mg/kg.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The Examiner is guided in his opinion that Applicant has not adequately described the presently claimed subject matter by the MPEP at § 2163 - 2163.05. In particular, while Applicant's specification as originally filed contains disclosure of methotrexate (1 mg/kg) administered around the injured nerve roots (total dose 2 mg/kg), such does not entitle Applicants to now claim a dosage range of "not to exceed a total dose of 2mg/kg each day" because such represents a dosage subgenus that was not previously set forth or that would have been immediately envisaged by one skilled in the art from the specification as originally filed. "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)"(emphasis added), see MPEP § 2163(I)(A). Also, "See also *In re Smith*. 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) ('Whatever may be the viability of an inductive-deductive approach to arriving at a claimed subgenus, it cannot

be said that such a subgenus is necessarily described by a genus encompassing it and a species upon which it reads.' (emphasis added)).", see MPEP § 2163.05(II).

Considering the teachings provided in the specification as originally filed, the Examiner finds that Applicants have failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set for the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicants had possession of the concept of administration of methotrexate in a dose "not to exceed a total dose of 2 mg/kg each day".

Claim1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, "into the spinal cord but not the brain" (present claim 1) is a concept that was not present in the specification as originally filed.

Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. The administration of methotrexate intrathecally "into the spinal cord but not the brain" is not specifically recited in the instant specification. Regarding applicants' assertion that the Anatomy and Physiology text, Human Anatomy and Physiology, second edition, pages 404-405 teach that the circulation of the cerebrospinal fluid through the brain ventricles is designed such that

only a very small amount of the CSF from the ventricles circulates into the central canal of the spinal cord, this lacks written basis as filed for such a limitation, because the text, Human Anatomy and Physiology, has neither been incorporated by reference in the instant application, nor has the brain administration negative limitation been disclosed as instantly filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberlain et al. (Archives of Neurology) and Biomethodology of the Rat (U).

Chamberlain et al. teach administration of methotrexate to patients with leptomeningeal metastases presenting with radiculopathy (see abstract). Methotrexate is administered intraventricularly in doses of 2 mg daily (total dose of 40 mg) (see page 508, column 1). Chamberlain et al. teach the same composition of methotrexate in the same dose to be useful in treatment of leptomeningeal metastases with radiculopathy.

The prior art differs in that it does not teach intrathecal administration into the spinal cord. However Chamberlain et al. teach intraventricular administration. The definition of intrathecal administration from Stedman's Medical Dictionary, 27th edition is administration within either the subarachnoid or the subdural space. Since the method of administering an agent intrathecally can mean that the agent is administered into the subarachnoid or subdural space, the method of administering intrathecally overlaps with Chamberlain's method of administering intraventricularly to treat leptomeningeal metastases with radiculopathy. Applicant has added the limitation that the injection site is intrathecally into the spinal cord but not the brain. However, there does not appear to be a basis for this exclusionary proviso in the instant case (see above). Regarding the location of the injection, an intrathecal injection of the instant claims is obvious over the intraventricular injection of the prior art. Applicant's reference provided on May 11, 2006

teaches that "once produced, cerebrospinal fluid (CSF) moves freely through the ventricules. Some CSF circulates from the ventricles into the central canal of the spinal cord. Although the prior art administers methotrexate for treatment of leptomeningeal metastasis, it provides relief of the symptoms, such as radiculopathy, and as such, it is reasonable and self-evident that methotrexate must treat the radiculopathy in each case, whether explicitly recognized or not. It would have been made obvious to one of ordinary skill in art at the time it was made to administer methotrexate in a dose of 1 mg/kg and not greater than 2 mg/kg each day to reduce lower back pain with radiculopathy motivated by the teaching of Chamberlain et al. who teaches that methotrexate is effective at a dose of 2 mg administered intraventricularly to treat leptomeningeal metastasis with radiculopathy. Chamberlain administers 2 mg/day methotrexate to a human patient who has leptomeningeal metastasis with radiculopathy, and the radiculopathy is resolved. The instant claims are drawn to an animal. When one looks that the specification for clarification of the animal, page 7 of the instant specification identifies the animal as a rat. The claim states that dosages of 1 mg/kg are to be administered, but does not state the frequency of the administration. Since the claim further states that a dose of not more than 2 mg/kg each day is to be employed, one can surmise that the dose of 1 mg/kg is to be given twice a day. In Biomethodology of the Rat (U) the weight of a laboratory rat is from about 250 grams to about 800 grams. To convert this weight to a dose that fits the claim, an 800 gram rat would receive 0.8 mg of methotrexate, not to exceed 1.6 mg of methotrexate (800

grams = 0.8 kg x 1 mg/kg = 0.8 mg x 2 doses = 1.6 mg per day. Chamberlain administers 2 mg/day.

Response to Arguments

Regarding the location of the injection, an intrathecal injection of the instant claims is obvious over the intraventricular injection of the prior art. Applicant's reference provided on May 11, 2006 teaches that "once produced, cerebrospinal fluid (CSF) moves freely through the ventricules. Some CSF circulates from the ventricles into the central canal of the spinal cord. Applicant asserts that as such the concentration of methotrexate achieved would not be expected by one of skill in the art to be as high as could be achieved through direct administraton into the spinal cord. It is noted that the features upon which applicant relies (i.e., the concentration of methotrexate in the CSF) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. The intraventricular dose of methotrexate of Chamberlain circulates into the spinal cord, thus the intraventricular administration of methotrexate of the instant claims does not patentably distinguish over the intraventricular dose of Chamberlain. Applicant asserts that the mg/kg dose instantly recited would be understood by one of skill in the art because of the need to understand how efficacy is related to safety in any particular species and the ability to extrapolate doses across different species. These are features that applicant relies on but are not claimed.

Applicant asserts that what is being treated with the methotrexate is the cancer, not the radiculopathy, and Applicant stresses that although two of the patients presented with radiculopathy, nowhere does this paper teach or suggest that symptoms of radiculopathy specifically are reduced when methotrexate is administered. In response, although the prior art administers methotrexate for treatment of leptomeningeal metastasis, it provides relief of the symptoms, such as radiculopathy, and as such, it is reasonable and self-evident that methotrexate must treat the radiculopathy in each case, whether explicitly recognized or not.

Regarding applicant's assertion that the dose would be 0.029 mg/kg/day based on a 70 kg individual, Chamberlain administers 2 mg/day methotrexate to a human patient who has leptomeningeal metastasis with radiculopathy, and the radiculopathy is resolved. The instant claims are drawn to an animal. When one looks that the specification for clarification of the animal, page 7 of the instant specification identifies the animal as a rat. The claim states that dosages of 1 mg/kg are to be administered, but does not state the frequency of the administration. Since the claim further states that a dose of not more than 2 mg/kg each day is to be employed, one can surmise that the dose of 1 mg/kg is to be given twice a day. In Biomethodology of the Rat (U) the weight of a rat is from about 250 grams to about 800 grams. To convert this weight to a dose that fits the claim, an 800 gram rat would receive 0.8 mg of methotrexate, not to exceed 1.6 mg of methotrexate. Chamberlain administers 2 mg/day. One of ordinary skill in the art would understand that depending on the malady, methotrexate is dosed in mg/m2 or it is dosed empirically, in 1 or 2 mg doses. In Chamberlain et al., the

methotrexate is dosed empirically, at 2mg /day dosed intraventicularly. The dosing of methotrexate would vary depending upon the malady being treated, the method of administration, the salt of the drug, and co-administration with other agents, such as leucovorin.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe
Patent Examiner
Art Unit 1614

June 13, 2007